REMARKS

Claims 1-3, 6-14 and 20-27 are pending in the subject application.

Objection to the Specification

In the March 22, 2007 Office Action the Examiner objected to the specification, claiming the proper naming for sequences should look like "SEQ ID NO:1" or "SEQ ID NOs:1-2".

In response, applicant has hereinabove amended the specification to correct the proper naming for sequences. Applicant maintains that these amendments to the specification do not raise any issues of new matter, and that these amendments are supported by the specification as originally filed. Accordingly, applicant respectfully requests the Examiner to remove this objection to the specification.

Rejection Under 35 U.S.C. §112

In the March 22, 2007 Office Action, the Examiner rejected claims 1-3, 6-14, and 20-27 under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner alleged that the claim(s) contains subject matter, which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner further alleged that claim 1, as amended presents a new matter issues because the amendments do not find support in the specification. Specifically, the Examiner alleged that in claim 1, as amended, the language "trimeric fusion protein containing three ligand binding domains, wherein said trimeric fusion protein has an increased binding affinity to a ligand than a monomeric ligand binding domain", constitutes new matter. Furthermore, the Examiner alleged that claims 2, 3, 6-14, and 20-27 are included in this rejection because they depend rejected independent claim 1 and do not cure the deficiencies under the instant rejection.

In response to the Examiner's rejection, applicant respectfully traverses on the ground that support in the specification can be found for claim 1, as amended, specifically for the above-referenced phrase.

There is no *in haec verba* requirement for newly amended claims in order to meet the written description requirement under 35 U.S.C. §112 first paragraph, rather, these claim limitations may be supported in the specification through implicit or inherent

disclosure. MPEP §2163 I.B. Furthermore, the standard for determining compliance with 35 U.S.C 112 first paragraph, requires a factual inquiry as to whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as claimed. MPEP §2163.02. Again, the subject matter of the claim need not be literally described in order for the disclosure to satisfy the description requirement. *Id.*

Briefly, pending claim 1 recites a method for generating a secreted disulfide bond-linked trimeric fusion protein, comprising (a) creating a DNA construct comprising a transcriptional promoter linked to a template encoding a fused protein subunit comprising a signal peptide sequence followed by in-frame fusion to a non-collagenous polypeptide comprising a ligand binding domain, which in turn is joined by in-frame fusion to a mammalian polypeptide which is heterologous from the non-collagenous polypeptide and which is capable of self trimerization said fused protein subunit to form said disulfide bond-linked trimeric fusion protein containing three ligand binding domains, wherein sad trimeric fusion protein has an increased binding affinity to a ligand than monomeric ligand binding domain; (b) introducing said DNA construct into a eukaryotic cell; (c) growing said host cell in an appropriate

growth medium under physiological conditions to allow said fused protein subunits to trimerize into the disulfide bond-linked trimeric fusion protein and to further allow the secretion of the trimeric fusion-protein; and (d) isolating said secreted trimeric fusion protein from the culture medium of said host cell.

As illustrated below, applicant respectfully asserts that support for amended claim 1 exists in several locations in the specification. Initially, applicant directs the examiner to the following excerpt which states:

> In contrast to the Fc Tag technology (Sledziewski et al., 1992 and 1998), with which secreted dimeric fusion proteins can be created, this timely invention disclosed herein enables the creation and secretion of soluble trimeric fusion proteins for the first time. Given the fact that a homotrimer has 3-fold symmetry, whereas a homodimer has only 2-fold symmetry, the two distinct structural forms theorectically can never be perfectly overlaid (Fig 1). As such, neither the homodimeric soluble TNF-R-Fc (e.g. Enbrel), nor the soluble CD4-Fc fusion proteins, could have had an optimal interface for binding to their corresponding homotrimeric ligands, TNF-α and HIV gp120, respectively. In contrast, homotrimeric soluble TNF receptors and CD4 created by the current invention are trivalent and structurally have the potential to perfectly dock to the corresponding homotrimeric ligands. Thus, these trimeric soluble receptor analogs can be much more effective in neutralizing the biological activities of their trimeric ligands.

Summary of the Invention, page 11, line 10 through line 22.

Applicant respectfully asserts that the above-referenced portion of the specifications provide proper support for amended claim 1, especially in light of the above-mentioned standard, created by MPEP §2163 I.B. Applicant ergo asserts that the present invention, as described above, illustrates a trimeric fusion protein that possesses the ability to perfectly dock to its corresponding homotrimeric ligands. The present invention allows for perfect docking with the homotrimeric ligand because both contain 3-fold symmetry (i.e. three binding domains), therefore providing two similar structural forms.

Although prior art dimeric fusion proteins can be shown to have increased affinity to their corresponding homotrimeric ligand, they are inherently less than perfect to dock with the corresponding homotrimeric ligands as dimeric fusion proteins possess only a two-fold symmetry (i.e. two binding domains). Therefore, the above-referenced specification reasonably conveys to one skilled in the art that the applicant described a trimeric fusion protein with three ligand binding domains in original specification as filed, because the only possible way the present invention could perfectly dock with the corresponding homotrimeric ligand is for the trimeric fusion protein to possess three ligand binding domains.

Additionally, applicant directs the examiner to the following excerpt which states:

> The result shown in Fig. 4 clearly indicated that the trimeric soluble TNF-RII-C-propeptide fusion proteins are extremely potent in neutralizing the TNF-α mediated apoptosis of WEHI-13VAR cells in the presence of Actinomycin D (500 ng/mL) (Sigma). When human TNF-α (R & D Systems) was used at 0.5 ng/mL, the trimeric soluble TNF-RII-T2 (both from serum-free media or in purified form) had an apparent Ki-50 (50% inhibition) of about 2 ng/mL or 8 X 10^{-12} M (assuming the MW of 240 kDa as homotrimer). This affinity to TNF-α is 4 orders of magnitude higher than that of the monomeric TNF-RII and at least 10-100 times higher than that of the dimeric soluble TNF-RII-Fc fusion, such as Enbrel (Mohler et al., 1993).

Description of the Invention, page 24, line 19 through page 25, line 4.

Applicant stresses that the current invention predicts theoretically, that a trimeric fusion protein with three ligand binding domains should have an even higher affinity to the corresponding homotrimeric ligand, than that of a dimeric fusion protein with only two ligand binding domains. It can be shown, that a fusion protein with two ligand binding domains, in comparison to a protein with only a monomeric ligand binding domain, can have an increased affinity to a corresponding homotrimeric ligand. Therefore, one skilled in the art would logically conclude the following:

1) If the affinity of a fusion protein with two ligand binding domains (dimer) to a corresponding homotrimeric ligand is greater than the affinity of a protein with one ligand binding domain (monomer) to the same corresponding homotrimeric ligand; and
2) If the affinity of a fusion protein with three ligand binding domains (trimer) to a corresponding homotrimeric ligand is greater than the affinity of a fusion protein with two ligand binding domains (dimer) to the same corresponding homotrimeric ligand;
3) Therefore, the affinity of a fusion protein with three ligand binding domains (trimer) to a corresponding homotrimeric ligand must be greater than the affinity of a protein with one ligand binding domain (monomer) to the same corresponding homotrimeric ligand, as illustrated in claim 1.

Furthermore, Applicant submits that the above-referenced portion of the specification provides direct support for amended claim 1. Applicant asserts that this example distinctly displays the increased affinity of the present invention to the corresponding homotrimeric ligands versus a protein with a monomeric ligand binding domain as illustrated in claim 1, or dimeric fusion proteins as asserted by the applicant. This example further

expands on the above-referenced specification in the *Summary of the Invention* section, wherein the only possible way for the present invention to display increased affinity over the dimeric fusion protein when binding to the homotrimeric ligand, is for the present invention to possess three ligand binding domains. Therefore, these results, as stated in the specification are evidence of support for amended claim 1.

In view of the applicant's arguments specifically illustrating support for amended claim 1 in the specification, applicant respectfully requests the Examiner to remove this ground of rejection.

No fee is deemed necessary in connection with the filing of this Amendment. If any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account 12-0115.

Respectfully submitted,

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